PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Scott AROUH, et al.

Serial No.: 09/611,220 — Group Art Unit: 1631

Filed: July 6, 2000 — Examiner: Allen, M.

For: **NEURAL-NETWORK-BASED IDENTIFICATION, AND APPLICATION, OF GENOMIC INFORMATION PRACTICALLY RELEVANT TO DIVERSE BIOLOGICAL AND SOCIOLOGICAL PROBLEMS, INCLUDING DRUG DOSAGE ESTIMATION**

Atty's Docket No.: DIA 0002P

San Diego, California
October 20, 2003

APPELLANT'S APPEAL BRIEF (37 C.F.R. §1.192)

Mail Stop APPEAL BRIEF
Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This BRIEF, the time for the filing of which is extended by the accompanying Petition, is in furtherance of the Notice of Appeal timely filed in this case on May 19, 2003.

The fees required under 37 C.F.R. §1.17(f) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This BRIEF is transmitted in triplicate.

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that these documents and the associated divisional patent application are being deposited with the United States Postal Service in an envelope addressed to the: Box APPEAL BRIEF, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date written below.

October 20, 2003	William C. Fuess	William C. Fuess
Date	Typed Name of Person Mailing Correspondence	Signature of Person Mailing Correspondence

This BRIEF contains items under the following headings and in the order set forth below.

1. Status of Claims
2. Status of Amendments
3. Summary of Invention
4. Issues
5. Grouping of Claims
6. Arguments
7. Reference to Attached Appendix
8. Real Party in Interest
9. Identification of Other Appeals and/or Interferences
10. Status of the Application Not Abandoned
11. Concluding Remarks

1. Status of Claims

Claims 10 and 14-15 are pending in the application. [Claim 9 is withdrawn from consideration by the Examiner, and Applicants wish to cancel this claim, but this claim has not been, will not be, and cannot be canceled by Applicants **until** entrance of Applicants' Amendment Under Rule 116 of March 19, 2003, which Amendment has **not** been entered by the Examiner.]

The rejections of claims 10 and 14-15 are appealed.

In the following enumeration of the rejections, the **order** of rejections appearing in the second and final Office Action of November 19, 2002 -- (1) rejection of claim 10 under 35 U.S.C. §112, second paragraph; (2) rejection of claims 10 and 14-15 are rejected under 35 U.S.C. §112, first paragraph; and (3) rejection of claims 10 and 14-15 under 35 U.S.C. §112, second paragraph -- is **changed**. The **order** (only) is so **changed** not only so as to group rejections under the same statutory section together, but because one (only) objection -- that of claims 10 and 14-15 under 35 U.S.C. §112, first paragraph -- appears to constitute the gravamen of the Examiner's arguments re: non-patentability.

In particular, claims 10 and 14-15 are rejected under 35 U.S.C. §112, first paragraph, for containing subject matter found by the Examiner to be lacking enablement in the specification disclosure, particularly that: "patient information required to train... [Applicants' claimed] neural network would not have been well known and readily available at the time of the invention" (Office Action of November 19, 2002, at page 4, lines 9-11).

Claim 10 was further rejected under 35 U.S.C. §112, first paragraph, for containing (only) **after amendment** such new/undisclosed matter as was found to have been inserted by action of Applicants' (First) Amendment of August 23, 2002.

Claims 10 and 14-15 were further rejected under 35 U.S.C. §112, second paragraph, for being indefinite, particularly for making reference to claim 9 [which claim 9 is not canceled until such time as Applicants' Amendment Under Rule 116 of March 19, 2003 -- which Amendment has **not** been entered by the Examiner -- should be entered, at which time claims 14-15 would be simultaneously amended to depend upon claim 10.

Claim 10 was further rejected under 35 U.S.C. §112, second paragraph, for being found to be confusing, particularly in use of the word "including", with the Examiner citing MPEP §2173.05(d).

2. Status of Amendments

Historically, after (1) a Requirement for Restriction mailed October 1, 2001, and (2) Applicants' election in response thereto of November 1, 2001, only (3) Applicants' [First] Amendment Under 37 C.F.R. §1.115 of July 2, 2001, has (so far) been entered.

Applicant's Amendment Under Rule 116 (i.e., amendment after final rejection) did **not** seek to substantively amend claim content, but only to cancel claim 9 so that the dependencies of claims 14 and 15 might be amended, and primarily sought **only** reconsideration of the Examiner's continuing rejections. This amendment has **not** been entered.

3. Summary of Invention

As may be read in the Abstract of Applicants' specification, Applicants' invention entails the (i) construction (programming), and (ii) training on historical data, of **neural networks**. The historical data suitable to train such neural networks -- the availability of which data will prove to be important to the Board in its consideration of the Examiner's rejection under 35 U.S.C. §112, first paragraph -- deals with relating the (i) alleles of each of a large number of individuals (patients) to the (ii) clinical responses of these same large number of individuals (patients).

Applicants' neural networks show when trained which alleles are, in combination, practically pertinent to a wide range of biological, social and clinical variables. Applicants' trained neural networks may be exercised to predict, in consideration of the genomic data of an individual patient, the response of the individual patient to any of the biological, social and clinical variables for which the neural network was trained.

Most particularly usefully, any of (1) optimal drug dosage, (2) drug dosage sensitivity, (3) expected outcome(s), and/or (4) adverse side effects may can be predicted. Both the human and economic costs of both optimal and sub-optimal drug therapies may be extrapolated from the exercise of various optimized and trained neural networks. Although not intended to prescribe drugs, nor even to set prescription drug dosage, Applicants's trained neural networks are very sophisticated and authoritative "helps" to physicians, and to physician reviewers, in answering "what if" questions.

As presently restricted, Applicants' claims 10 and 14, 15 under appeal are particularly directed to a "method of predicting a therapeutically optimal drug dosage for a particular individual patient in respect of alleles and/or characteristic SNP pattern genomic data of the particular individual patient" (Preamble of Claim 10, as amended).

4. Issues

4.1 Rejections Under 35 U.S.C. §112, First Paragraph

Are Applicant's claims 10 and 14-15 unpatentable under 35 U.S.C. §112, first paragraph, because, as the Examiner states: "the information required to practice the [claimed method of the] invention is not available, and does not exist" (Office Action of April 23, 2001)

OR

are (1) Applicants' assertions in their Amendment response of August 23, 2003, that:

> "In fact, (i) such information does exist, and (ii) is well known to practitioners of the art to which the invention pertains. Further, (iii) equivalent information regarding "genomic data including alleles and/or characteristic SNP patterns" to that which is suitable for use in the present invention **has** before the filing date of Applicants application been used to realize "Pharmogenetic prediction of clozapine response" [citing an paper previously supplied the Examiner].... Still furthermore, (iv) using publicly available data regarding "genomic data including alleles and/or characteristic SNP patterns", Applicants have reduced their own invention to operative practice."

combined with (2) Applicants' submission of an AFFIDAVIT in their Amendment Response Under Rule 116 of March 3, 2003, stating:

> "Applicants submit the attached AFFIDAVIT UNDER 37 C.F.R. §1.132 of Dr. Nicolas Schork, University of California, San Diego (having such qualifications as are set forth in paragraph 1. of the AFFIDAVIT). This AFFIDAVIT should suffice to explain to the Examiner why her views as to the supposed unavailability (at the July 6, 2000, time of application filing) of genomic data upon which Applicants' claimed method operates are flawed. In fact, (i) this information did and does exist, and (ii) is well known to practitioners of the art to which the invention pertains."

sufficient **in combination** to **refute** the unsubstantiated, unsupported and apparently personal opinion of the Examiner that data sufficient to train Applicants' neural network was neither available nor obtainable by a practitioner in the biogenomics art of the invention without undue experimentation as of the

application filing date of July 6, 2000.

4.2 Rejection of Claim 10 Under 35 U.S.C. §112, First Paragraph

Is claim 10 properly rejected under 35 U.S.C. §112, First Paragraph, in the Examiner's office Action of November 19, 2002, for containing new matter found to have been inserted by Applicants' Amendment of August 23, 2002,

OR

being that Applicants' maintain their amendment of August 23, 2002, only served to amend claim 10 but modestly so as to improve clarity without changing the scope or limitations thereof, is this rejection -- newly made only after Applicants's amendment and maintaining that (only) the amendatory language is unsupported by the specification -- unsound.

4.3 Rejection of Claims 14-15 Under 35 U.S.C. §112, Second Paragraph

Are claims 14-15 properly further rejected under 35 U.S.C. §112, second paragraph, for being indefinite for making reference to claim 9, not canceled until Applicants' Amendment Under Rule 116 of March 19, 2003, should be entered while this Amendment has **not** been entered by the Examiner,

OR

should Applicants' Amendment Under Rule 116 and/or an Examiner's Amendment changing the dependencies of claim 14 and 15 from claim 9 to claim 10 **simply** be entered, amending these claims 14 and 15 to (properly) depend upon claim 10.

4.4 Rejection of Claim 10 Under 35 U.S.C. §112, Second Paragraph

Is claim 10 properly rejected under 35 U.S.C. §112, Second Paragraph for use of the word "including" as alleged by the Examiner citing MPEP §2173.05(d),

OR

is the term permissible, including under MPEP §2173.05(d).

5. Grouping of Claims

Arguments made in section 6.1 hereinafter as regards the basis for rejection under 35 U.S.C. §112, First Paragraph, apply to claims 10 and 14-15 so rejected, in common.

Arguments made in section 6.2 hereinafter as regards the basis for rejection under 35 U.S.C. §112, First Paragraph, apply to claim 10 so rejected.

Arguments made in section 6.3 hereinafter as regards the basis for rejection under 35 U.S.C. §112, Second Paragraph, apply to claims 14 and 15 so rejected, in common.

Arguments made in section 6.4 hereinafter as regards the basis for rejection under 35 U.S.C. §112, Second Paragraph, apply to claim 10 so rejected.

6. Arguments

6.1 Rejection of Claims 10 and 14-15 Under 35 U.S.C. §112, First Paragraph

The Examiner finds Applicants' specification non-enabling under 35 U.S.C. §112, First Paragraph, and accordingly rejects all pending claims 10 and 14-15 under 35 U.S.C. §112, First Paragraph.

The Examiner negates, for reasons given below, Applicants' several showings, discussed below, in their Amendment of August 23, 2002. The Examiner **continues** to maintain, as stated in her very First Office Action, "that the information required to practice the [claimed method of the] invention is not available, and does not exist." (First Office Action of April 23, 2001)

In Applicants' Amendment response of August 23, 2003, Applicants told the Examiner: "In fact, (i) such information does exist, and (ii) is well known to practitioners of the art to which the invention pertains.

Applicants explained:

> "The 'raw material' of Applicants' invention is (1) human genetic information, along with (ii) physiological data which has been around ever since humans have been

around. To get relevant DNA from a person, one does not need blood. Indeed, we are continuously shedding DNA through hair loss, skin flaking, saliva, etc. To get somebody's DNA is not very hard. For this specific claim, if Applicants operating as a company wanted to get DNA then they would just follow around people with a certain drug side effect and vacuum up the dermis that their body gives off. Medical chart data could be gotten in an interview. True, to extract the DNA would take a little bit of lab work, but the techniques involved have been automated since the late 1980's and the level of knowledge required would be a high school education.....

"While biobanks that contained patient information sprang up in the late 1990's, there have been several sample repositories (i.e. blood sample and patient information) through the National Institutes of Health and private institutes such as the HUGO working group. See (http://ariel.its.unimelb.edu.au/~cotton/discuss.htm). These biobanks that **have been around before the present application was filed**....

Applicants cite **specifics**:

"Finally, at the time of the application filing, there were numerous private researchers at universities or institutes who maintained the necessary information to execute the [method of the] patent described here, and the only barrier is money. One such example is John Kelsoe, professor of medicine at the University of California, San Diego, who has maintained a blood sample databank with associated patient information on lithium in bipolar patients (with the adverse effect of the drug being obesity) since 1989....

"[L]et us examine specific examples that will remove once and for all any doubt that there was the information required for enablement of Applicants' claimed invention. Please note that if the Examiner chooses to refute these examples, then the Examiner may have to allege her superior domain knowledge or relevant skill level and/or the state of the art at the time of the submittal of Applicants' application.

"First, let us look at the information submitted previously. The 'Hypertension Response Prediction' NSF Final report was submitted well after the application filing. It was submitted to show that patient genotype-phenotype patient information was available. Applicants' company Prediction Sciences, Inc. licensed this specific information from Pharsight, Inc. in January of 2001. However, Pharsight in turn licensed the data from Duke University over the course of 1999, which shows data was available at the time of the patent application, if an

> individual or organization had the financial wherewithal to obtain it."

Applicants now wish within this Appeal Brief to **add** information developed **after** the March 19, 2003, filing date of their most recent Amendment. In so doing, Applicants admit to the evidentiary limitations of their next following assertions, which are admittedly both (i) newly presented, and (ii) not presented under separate AFFIDAVIT.

However, Applicants wish to bring the following **new** information to the attention of the Board solely so that the Board might hesitate to **dis**regard the above statement that "Pharsight in turn licensed the data from Duke University over the course of 1999, **which shows data was available at the time of the patent application**". (boldface added)

Namely, in private communications with Mr. H. Gilbert Smith of Duke University, Applicants are now informed that "[T]he data Pharsight provided came from the Duke University Coronary Syndromes -- Congestive Heart Failure database, that was licensed by Duke to Pharsight effective February 24, 2000. That license terminated on February 24, 2002, but that termination has no effect on the rights of any Pharsight customer to continue to use the data in accordance with the terms agreed between the customer and Pharsight" (Private E-mail communication to inventor Cornelius Diamond dated March 21, 2003.)

In simplest possible terms, data suitable for use in Applicants' claimed method **was already available** at the time of the application filing. In simplest possible terns, Applicants used this very data to successfully implement their own invention.

However, due to possible evidentiary problems with this showing (only), the effect of such particular data (i.e., the database from Duke University) on this appeal might be uncertain **if** it was the **only** such data. In actual fact, it is but one of many sources of such data, as will now be further developed.

First, Applicants had, and have used, such data (pre-existing before July 6, 2000), **themselves**.

> "The Examiner states "Page 30 [of Applicants' Amendment] documents that the biggest hurdle was obtaining the patient data source and that cost prevented the inventors for {from} generating a patient pool designed for the study." With all due respect, this is ABSOLUTELY NOT what page 30 says at all. Page 30 states that while Applicants "were forced to sort through over 1200 patient charts by hand... to obtain the patients that met Applicants' protocol for inclusion in this study" it also states Applicants " successfully surmounted this obstacle to bring this study to conclusion on-time".
>
> "This is just further evidence that such a task can be done. In fact, it **was** done by the Duke researchers who gathered the data pre-2000 for Pharsight, Inc. and Applicants just made it better FOR THEIR SPECIFIC PROTOCOL."

In simplest possible terms, Applicants state that they have successfully delivered (to the National Institute of Health) results obtained from their **own** claimed method using **exactly** such data, available **before** July 6, 2000, as the Examiner asserts was **not** so available.

Applicants state:

> "The Examiner further states that "the document concerns the instant invention and acknowledges on page 5 that a great deal of software and data preparation had to be invented in order to successfully execute the method". In this case the Examiner is making a false assumption based on lack of knowledge of software development. What is claimed and taught in the instant invention is a methodology for predicting adverse effects; on page 5 what was done was "-Pre-processing sorting and annotating SNP software created" This has to do with putting the raw data into a database program and has nothing to do with the instant invention; "Advanced neural network routines developed on MATLAB environment" This has to do with implementing our algorithms that Prediction Sciences had ALREADY CREATED at the time of the instant invention on the MATLAB platform, which is a software development process called porting to a new platform (i.e. coding in a new computer language) and is not claimed anywhere in the instant invention; "Neural network algorithms validated on NCI AML/ALL gene expression data" Here Applicants just used what they had already invented on a publicly available dataset (available since 1999: Golub et al. (1999). Molecular classification of cancer: class discovery and class prediction by gene expression

monitoring, *Science*, Vol. 286:531-537);"Novel Bayesian thresholding technique invented" This is a pre-processing data technique nowhere referred to in the instant invention; And"Novel Functional Partitioning Method invented for future neural network design" This is a neural network architecture nowhere referred to in the instant invention.

"The Examiner further goes on to say that data from Pharsight and Genaissance would not be available to one skilled in the art. As to the former the Examiner has been proved wrong, as one could license the data from its source, Duke University; and as to the latter their information came from university studies, which are done by someone "with ordinary skill in the art".

"The Examiner makes the further unsubstantiated claim that these studies would not have included all the information necessary for the method claimed. Unless the Examiner is prepared to show otherwise, the applicant states that patient studies have been done for decades and are designed by people trained to run them, i.e. those with "ordinary skill in the art". The information is drug(s) taken (maintained as a matter of record, obvious); drug dosages and/or efficacy data (in patient chart medical records which is part of any drug study) adverse event(s) (also in patient medical records); genomic data (gained as a tissue or blood sample and then genotyped by techniques that have been around for at least two decades at the time of this writing).

"Applicants maintain that a person with ordinary skill in the art could have run a study to gain the necessary information for the instant invention. To back up this claim, Applicants have submitted the following affidavit from Dr. Nicholas Schork who clearly refutes the assertions of the Examiner.

"The Examiner further asserts that Applicants "investigated a known pathway with known genomic markers and known drugs for treatment" and that "it would have been more difficult to determine such associations for uncharacterized pathways with no known genomic marks {markers} and known drugs for treatment". This statement is puzzling, as Applicants wonder if the Examiner is asserting that an invention has to completely elucidate the mechanism behind the problem it solves? If this is the case, the Examiner might want to invalidate nearly all patents dealing with objects involved in a nonlinear mechanism, i.e. electrical, aeronautical, chemical power systems, etc. as the physics of these systems is still largely unknown today. In addition, the patent Examiner might want to invalidate all drug patents, as the mechanism of action is largely not proven in a large percentage of current drug therapies. If it were, the medicine would work the same in everybody, which took the drug, negating the need for the instant invention.

"The incongruity of the previous statements suggest that the Examiner should take a closer look at what is being claimed in the instant invention, which is a methodology to build a predictor of adverse events, drug dosage, drug efficacy, and/or some clinical outcome of interest, NOT the solution to all biological problems and/or questions! As to the availability of markers, Applicants remind the Examiner that a 'working draft' of the human genome was completed on June 26, 2000 and therefore all SNP markers (patterns of which Applicants reference in the instant invention) of interest (i.e. in genomic coding regions) were technically known at this time.

"The Examiner still further asserts that this is a complex problem, and that a person skilled in the art would have trouble implementing such. Applicants agree that this is a complex problem with many facets and is non-obvious; ergo, the reason why Applicants submitted the patent in the first place to teach those skilled in the art! If the Examiner has a problem with "the computational complexity of such a situation" Applicants suggest to the Examiner to [consider] those accompanying claims which the Examiner restricted as separate inventions in her first office action.

"The Examiner states "Associations of alleles to responders or non-responders is {are} not analogous to the claimed method for predicting optimal drug dosage and/or drug efficacy for an individual patient. As such, arguments with respect to Arranz et al is {are} not persuasive." Applicants agree that the method is different from the claimed method, which is the reason for the instant invention! Applicants remind the Examiner that Exhibit B of Applicants' predecessor amendment was given to refute the claim that "the information required to practice the [claimed method of the] invention is not available, and does not exist" from the first office action mailed April 23, 2002.

"Furthermore, if the Examiner read the article it shows the investigator taking a candidate gene approach, taking previously UNKNOWN alleles and then correlating them with response in a linear fashion; our instant invention takes this much further by able to incorporate nonlinear associations as well.

"As to the Examiner's assertion that the evidence provided does not have drug dosage data, Applicants wish to assure the Examiner that this is routine and since the study examined the phenotype of drug response, not dosage, this was not reported. Drug dosage is just one of the phenotypes that the instant invention claims as a methodology to build a predictor for.

"As stated many times previously, the instant invention is a methodology for computationally building a predictor of

> a clinical outcome of interest, and this information is gathered routinely in most clinical studies. If the Examiner has any doubt of this she should read the many references pertaining to previous pharmacogenomic studies given in the original patent application, as well as any drug advertisement in a common magazine.
>
> "Finally, the Examiner states various examples around the time of the instant invention of the difficulty of mapping traits to disease. Applicants again agree with the Examiner of this fact, and suggest that if the researchers quoted read Applicants patent [application], then they would have been alleviated of their uncertainty. The methodology claimed by the Applicants is most certainly NOT the haplotyping technique of Judson, et al. as this is just a technique of linear correlating clustered alleles on a single locus to disease phenotypes, with no regard to any nonlinear correlations that would reduce the number of alleles under study among other problems. The fact that the authors require massive amounts of haplotypes just further shows the need for the instant invention.

All the above single-spaced paragraphs are quoted from Applicants' amendment of March 19, 2003, with boldface added.

Applicants further stated:

> "Further, (iii) equivalent information regarding "genomic data including alleles and/or characteristic SNP patterns" to that which is suitable for use in the present invention **has** before the filing date of Applicants application been used to realize "Pharmogenetic prediction of clozapine response" [citing a paper previously supplied the Examiner].... Still furthermore, (iv) using publicly available data regarding "genomic data including alleles and/or characteristic SNP patterns", Applicants have reduced their own invention to operative practice."

The paper re: "Pharmogenetic prediction of clozapine response" is within the application file; the issue of Applicants' reduction of their invention to operative practice **using databases that the Examiner claims did not then exist** is discussed above.

Since the Examiner denied these showings (i)-(iv), discussing the same, and **continued** her rejection of claims 10 and 14-15 under 35 U.S.C. §112, first paragraph, Applicants also proceeded in their Amendment Under Rule 116 of March 19, 2003, to submit an AFFIDAVIT UNDER 37 C.F.R. §1.132 of Dr. Nicolas Schork, University of California, San Diego (having such arguably

impressive qualifications as are set forth in paragraph 1. of the AFFIDAVIT).

Applicants stated, and do now state:

> "This AFFIDAVIT should suffice to explain to the Examiner why her views as to the supposed unavailability (at the July 6, 2000, time of application filing) of genomic data upon which Applicants' claimed method operates are flawed. In fact, (i) this information did and does exist, and (ii) is well known to practitioners of the art to which the invention pertains....
>
> "Dr. Schork presents facts that "(1) patient genomic information sufficient to practice the invention, to wit: to train and to exercise the neural network, **was** available on 07/06/00, **and**, to the extent that the Examiner or any finder of fact should refute this my assertion, (2) this data might alternatively readily be obtained as of 07/06/00 by a practitioner of the genomic arts having but such routine skills as then existed, and without undue, and, indeed, with little or even **no**, experimentation". (Schork AFFIDAVIT paragraph 7.) These modes of (i) accessing, and/or (ii) obtaining genomic data were all **standard**, known and contemplated as of the time of application filing!...
>
> "Applicants' invention involves the arts of computer programming, and, the Examiner would maintain, the gathering of genomic data. In fact, it is the later that is **easier**. As explained by Dr. Schork: "The articles I now cite are prominent, their teachings clear and obvious, and any practitioner in the genomic data arts would have no problem in recognizing applicability of **both** (i) genomic data **already gathered (!!)**, and (ii) standard clinical methods of so gathering genomic data, to the claimed method of Applicants' invention. (Schork AFFIDAVIT paragraph 12.) (emphasis in original)"

Applicants stated:

> "The Examiners' finding that Applicants' showing of suitable data was in possession (at a time before filing) of both Genaissance and Pharsight is **un**convincing is respectfully traversed. If multiple parties in possession of what the Examiner would allege are **independent, and un-shared** databases appropriate to Applicants' invention is not evidence that such databases **can** be routinely constructed, what is?...
>
> Clearly Applicant now provides, in the form of materials previously submitted, and the Schork AFFIDAVIT, the required evidence. The Examiner has also misunderstood Applicants' evidence of the reduction of their invention to operative practice under contract with NIH. Although this

reduction does **not** conclusively mean that no further innovation, and/or undue experimentation, occurred in the time since July 6, 2000, in actual fact no such innovation and/or undue experimentation occurred, and Applicants' **successful** reduction to operative practice was in full accordance with their own specification!

Applicants argued:

> "In the case of the "genomic data including alleles and/or characteristic SNP patterns" (claim 10) that the Examiner finds so mysterious and unavailable to / unrealizable by (at least without undue experimentation) a practitioner of the genomic data acquisition arts, the Schork AFFIDAVIT makes clear:
>
> "It has been well-known that although there are many genes that influence the pharmacokinetic properties of individual drugs, there is a family of ~30 genes known as the cytochrome P450 (CYP450) gene family, characterized in 1982 (see, e.g., Gotor and Fujii-Kuriyama(1989)....
>
> "It is well known that there is a great deal of variation in CYP450 genes (see. e.g., Weber 1997, op cit.)....
>
> "The differences among individuals that result from this genetic variation can, and are known to, influence the function of CYP450 genes (see, e.g., Weber 1997, op cit.).
>
> "Since this family of genes is known to influence drug metabolism, and there are known to be variations in the genes in this family that influence metabolism of endogenous compounds, variation in these genes are likely to (and have been documented to) influence the amount of drug required to elicit a particular effect in different individuals....
>
> "Ultimately, if a practitioner did not know *a priori* which, e.g., CYP450 genes were involved in the metabolism of a particular drug, and further, which genetic variations in CYP450 genes influenced variation in drug metabolism (which is often the case), he or she could 'genotype' a number of individuals (i.e., assess which variant at a site in a gene individuals possess) who have been or are being treated with a particular drug who have also been administered different doses based on efficacy of the drug (a routine practice by physicians and clinicians), and then use algorithms like those taught in the patent application to determine which genetic variants influence dose effects among the individuals studied." Schork AFFIDAVIT paragraphs 23-27.

Simply put, Applicants claimed method will work on a public genomic database that was **pre-existing** at the time of application filing.

The Schork affidavit even dealt with **access** to this data. Applicants stated:

> "The Examiner may wonder about access to data. To publish in a journal the source data from which the investigative findings and/or conclusions are derived **must** be made available, on request, to anyone who wants it. The Schork AFFIDAVIT says:
>
> "This emphasis led to the creation of databases (see, e.g., Collins FS, Brooks LD, Chakravarti A (1998). A DNA polymorphism discovery resource for research on human genetic variation. Genome Research. 8:1229-31; Gu et al. 1998, op cit.; and Wang et al. 1998, op cit.) containing information about variation in human genes." Schork AFFIDAVIT paragraph 43.

Applicants still further argued:

> "The art of the creation of genomic databases is predictable, and even routine.
> As stated in the Schork AFFIDAVIT:
>
> "This emphasis [on identifying genetic variations] led to the creation of databases (see, e.g., Collins FS, Brooks LD, Chakravarti A (1998). A DNA polymorphism discovery resource for research on human genetic variation. Genome Research. 8:1229-31; Gu et al. 1998, op cit.; and Wang et al. 1998, op cit.) containing information about variation in human genes.
>
> "These databases are, and have been for years, publicly accessible such that any practitioner could query them." (Schork AFFIDAVIT paragraphs 43 and 44)....
>
> "If variations in the genes are found, then individuals who have been prescribed relevant drugs can be genotyped in an appropriate way (see, e.g., Ross P, Hall L, Smirnov I, Haff (1998). High level multiplex genotyping by MALDI-TOF mass spectrometry. Nature Biotechnology 16:1347-51.) and association studies can be pursued...." (Schork AFFIDAVIT paragraph 32).

The legal standard that the Board should consider is that same standard regarding which the Examiner was informed (with appropriate citation to the MPEP, and through the MPEP to the case law). Applicants stated that:

> "The examiner must then weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should never make the determination based on

personal opinion. The determination should always be based on the weight of all the evidence. (MPEP: 2164.05 Determination of Enablement Based on Evidence as a Whole)

Applicants submit that the explanatory Schork AFFIDAVIT is very weighty evidence indeed, and that, on the basis of this AFFIDAVIT alone, the Examiner's rejections of claim 10 and 14-15 under 35 U.S.C. §112, First Paragraph, should be overruled.

6.2 Rejection of Claim 10 Under 35 U.S.C. §112, First Paragraph

The arguments of section 6.1 above are incorporated within this section 6.2 by reference.

Requiring identification of support in the specification for the amended language in the (i) preamble and (ii) body of claim 10, the Examiner rejects amended claim 10 under 35 U.S.C. §112, First Paragraph for, apparently, incorporating new matter.

Claim 10 as originally presented stated:

10. A method of predicting an optimal drug dosage for a particular individual patient in respect of alleles and/or characteristic SNP pattern genomic data of the particular individual patient, the method comprising:

training a neural network on numerous examples of (i) alleles and/or characteristic SNP pattern genomic data, and corresponding (ii) historical drug dosage results including optimal drug dosages, for a multiplicity of patients so as to make a trained neural network that is fit, and that possesses a measure of goodness, to map (i) alleles and/or characteristic SNP pattern genomic data to (ii) drug dosage results including optimal drug dosages; and

exercising the trained neural network on the alleles and/or characteristic SNP pattern genomic data of the particular individual patient to predict an optimal drug dosage for the particular individual patient from among the optimal drug dosages to which the neural network was trained.

Claim 10 was amended as follows:

10. (Amended) A method of predicting a[n] <u>therapeutically</u> optimal drug dosage for a particular individual patient in respect of alleles and/or characteristic SNP pattern genomic data of the particular individual patient, the method comprising:

training a neural network on numerous examples of (i)

alleles and/or characteristic SNP pattern genomic data, and [corresponding] (ii) historical drug dosage results including optimal drug dosages, for a multiplicity of patients, which historical drug usage data are related to at least some of the genomic data, so as to make a trained neural network that is fit, and that possesses a measure of goodness, to map (i) alleles and/or characteristic SNP pattern genomic data to (ii) drug dosage results including optimal drug dosages; and

exercising the trained neural network on the alleles and/or characteristic SNP pattern genomic data of the particular individual patient to predict an optimal drug dosage for the particular individual patient from among the optimal drug dosages to which the neural network was trained.

Applicants find this amendment to their claim 10 to be entirely consistent with their invention as taught, which continually stresses the need for a therapeutical dosage. The first three sections of the original, parent, patent application should be referenced.

Secondly, the original, parent, patent application and the one that it references talk about optimizing training by genetic algorithms so this is a valid modification to help clarify the teaching process.

Thirdly, the reduction in computational complexity of said algorithm is clearly taught in the body of the instant patent application in section four.

No new matter is added.

6.3 Rejection of Claims 14-15 Under 35 U.S.C. §112, Second Paragraph

The arguments of sections 6.1 and 6.2 above are incorporated within this section 6.3 by reference.

Claims 14-15 properly further rejected under 35 U.S.C. §112, second paragraph, for being indefinite, for making reference to claim 9, not canceled until Applicants' Amendment Under Rule 116 of March 19, 2003.

Applicants maintain that this Amendment Under Rule 116 of

March 19, 2003, should have been entered for purpose of simplifying issues for this appeal, and should now be directed to be entered by the Board.

Should Applicants' amendment under Rule 116 and.or an Examiner's Amendment simply be but entered then it would an could amend these claims 14, 15 to (properly) depend upon claim 10. (As it stands, the rejection of claims 14, 15 does not affect the rejection(s) of claim 10, separately appealed and argued.)

This simple matter is arguably below the dignity of the Board, and should have been dealt with by the Examiner and Applicants' undersigned representative. Indeed, it can still be rendered moot by any statement in the Examiner's reply brief to the effect that claims 14 and 15 will be amended to be dependent upon claim 10, as requested by Applicants, conditional upon allowance of claim 10 by the Board.

6.4 Rejection of Claim 10 Under 35 U.S.C. §112, Second Paragraph

The arguments of sections 6.1 - 6.3 above are incorporated within this section 6.4 by reference.

Claim 10 is rejected by the Examiner under 35 U.S.C. §112, Second Paragraph for use of the word "including" as alleged by the Examiner citing MPEP §2173.05(d). MPEP §2173.05(d) does **not** support this proposition. The word "including" is an open-ended term often used in the body of a claim in lieu of the (preferred) claim transition word "comprising". It is so appropriately used in claim 10.

7. Reference to Attached Appendix

An appendix containing in plain text all the claims involved in this APPEAL is attached.

8. Real Party in interest

The real party in interest in this Appeal is Prediction Sciences, Inc., a California Corporation, as the assignee of all

inventors.

9. Identification of Other Appeals and/or Interferences

There are no other appeals or interferences known to the Appellant, nor to Applicant's undersigned legal representative nor to Applicant's assignee, that will directly affect, or be directly affected by, or have any bearing on, the pending appeal.

10. Concluding Remarks

Applicant argues that his invention **as** taught and claimed is (1) adequately enabled under 35 U.S.C. §112, First Paragraph, (2) that the dependencies of claims 14 and 15 should have been changed by the Examiner's entrance of Applicants' Amendment Under Rule changing these claims to depend upon claim 10 instead of claim 9, thereby to remove any indeterminacy under 35 U.S.C. §112, Second Paragraph. (3) that amendments to claim 10 do **not** constitute new matter, nor any such additional claimed matter as is not properly supported in the specification teaching, and that (4) use of the word "including" within claim 10 is permissible under 35 U.S.C. §112, Second Paragraph.

For these and other reasons, the claims of the present application are deemed allowable, and the determination of the Board to that end is respectfully solicited.

Sincerely yours,

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CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that these documents and the associated divisional patent application are being deposited with the United States Postal Service in an envelope addressed to the: Box APPEAL BRIEF, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date written below.

October 20, 2003	William C. Fuess	William C. Fuess
Date	Typed Name of Person Mailing Correspondence	Signature of Person Mailing Correspondence